REMARKS

The specification has been amended to correct omissions as required by the Examiner. Specifically, the empty spaces in paragraph [00120] on page 46 of the specification have been replaced with the serial numbers to the referenced U.S Patent Applications. Applicants respectfully assert that no new matter has been added and request entry of said amendments.

Claims 1-23 were pending in this application. Claims 11 and 17 have been withdrawn from consideration as being drawn to non-elected species. Applicants have amended claims 1, 5, 6, 7, 10, 12-16, and 19. Applicants have canceled claims 2-4, 8, 9, 11, 17, and 21-23 without prejudice. Support for the amendments can be found in paragraphs [0001], [0010]-[0012], [0018]-[0020], [0044]-[0051], and [0137]-[0145] of the instant specification.

Applicants reserve the right to pursue the subject matter of the withdrawn/canceled claims in a related application(s), without relinquishing the scope of the claimed subject matter.

The Examiner's Rejection Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn:

The Examiner has rejected claims 5 and 6 based on U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner states that the recitation of "epithelial and/or endothelial cell" is indefinite because it is unclear how to compare the survival of an epithelial cell to an endothelial cell. Solely in an effort to expedite prosecution, Applicants have amended claims 5 and 6. Applicants submit that the amendments clearly define the embodiments of claims 5 and 6 as relating to comparing treated and untreated cells of similar types. Applicants respectfully request that this rejection be withdrawn.

The Examiner's First Rejection Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn:

The Examiner has rejected claims 1-10, 12-16, and 17-23 based on U.S.C § 112, first paragraph as not complying with the enablement requirement. Specifically, the Examiner states that the specification does not reasonably provide enablement for a method of treating a hypoproliferative cell disorder or disorder involving increased cell death in a patient. Additionally, the Examiner states that the specification does not enable the use of the full scope of EphA2 antagonistic agents, as currently claimed. Applicants respectfully disagree.

The legal standard for the test for enablement is whether one of ordinary skill in the art could make and use the invention without undue experimentation, based on the teachings in the disclosure of the patent specification coupled with information that was known in the art at the time the patent application was filed see (U.S. v. Teletronics Inc., 8 USPQ2d 1217, Fed. Cir 1988).

Factors to be considered in determining whether experimentation is undue include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a), citing *In re Wands*, 858, F.2d 731, 737 (Fed. Cir. 1988).

No single factor is controlling, and the Examiner must consider all of the evidence related to each of the factors. MPEP § 2164.01(a). For example, the quantity of experimentation is merely one factor to be considered in determining whether experimentation is undue. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." MPEP § 2164.06, citing *In re Colianni*, 561 F.2d 220, 224 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

MPEP § 2164.06, citing *In re Wands*, 858 F.2d at 737 and *In re Angstadt*, 537 F.2d 489, 502-504 (CCPA 1976).

In addition, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. The Examiner is given the guidance that undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the relevant art at the time of filing. *Fields v. Conover,* 170 USPQ 276, 279 (CCPA 1971). Indeed, the Court of Customs and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 USPQ 214 (CCPA 1976), at 218-219:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, ... then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act. *Id.* at 219.

Thus, all that is required is that a reasonable amount of guidance with respect to the direction of the experimentation is provided; reasonable certainty with regard to the outcome of the experimentation is not required.

Applicants submit that the rejection is intended to encompass claims 1-10, 12-16, and 18-23, as claim 17 has been withdrawn from consideration as being drawn to a non-elected invention. Applicants also submit that the rejection with regard to claims 2-4, 8, 9, and 21-23 is moot in view of the cancellation of claims 2-4, 8, 9, 11, and 21-23.

Applicants respectfully submit that the present invention recognizes that antagonism of the EphA2 (Eck) protein could lead to an induction of proliferation, growth and survival of hypoproliferative cells. The EphA2 (Eck) protein has been well characterized as a member of the proto-oncogene class of receptor tyrosine

kinases (for example see U.S. Patent Serial No. 5,824,303 hereinafter "the '303 patent") and as such, was thought to play a role in carcinogenesis. Indeed, the overexpression of EphA2 in hyperproliferative cells, such as cancerous cells, results in a poor prognosis for the patient (for example see U.S. Patent Serial No. 6,927,203 entitled EphA2 As A Therapeutic Target For Cancer). As a result, it was suspected that antagonism of EphA2 would lead to cell death or a reduction in proliferation. In fact, Applicants have recognized that the opposite effect occurs – that antagonism leads to cell growth.

Accordingly, the scenario encompassed by the embodiments of the present invention relate to hypoproliferative cells, in other words, cells that do not grow and divide in a timely fashion to properly function in an organism. The EphA2 protein differs from many members of the receptor tyrosine kinase family by negatively regulating proliferation of metastatic cells (see Zantek *et al.* Cell, Growth and Differentiation 1999 10;629-638, hereinafter "Zantek"). Zantek also teaches that EphA2 also differs from other RTK family members by retaining enzymatic activity in the absence of ligand binding. This property of EphA2, namely its ligand independent enzymatic activity, has been exploited by the inventors by contemplating the development of EphA2 antagonists in an effort to induce proliferation growth and survival of hypoproliferative cells.

The Examiner maintains that for the therapeutic method to be predictable, the role of EphA2 expression/phosphorylation must play an inducing role in the proliferation of epithelial/endothelial cells. The Examiner cites Pandey *et al.* (IDS ref C219, hereinafter "Pandey") and Rosenberg *et al.* (IDS ref C241, hereinafter "Rosenberg") as evidence that the clinical value of the methods of the invention would be ineffective. Applicants respectfully disagree.

Pandey discloses a role for B61 (Ephrin-A1) in TNF-alpha induced angiogenesis as demonstrated by various experiments within the article. Specifically, the Examiner refers to the experiments in Figures 3 and 4 in support of the argument that an EphA2 antagonist (Anti-B61), could not lead to an increase of expression/phosphorylation in such a manner as to promote proliferation of epithelial/endothelial cells. Figure 3 represents an experiment in which Eck

autophosphorylation was determined in the presence of TNF-alpha alone, or TNF-alpha and anti-B61 antibodies. In the depleting B61 condition, TNF-alpha failed to induce autophosphorylation of Eck in HUVEC cells suggesting that this effect is mediated through B61. Figure 4 represents another B61 depletion experiment in which Hydron pellets impregnated with either TNF-alpha or bFGF with or without anti-B61 antibodies were implanted in murine corneas. The TNF-alpha and bFGF pellets stimulated a strong angiogenic response, whereas the plug containing TNF-alpha and anti-B61 antibodies resulted in a greatly attenuated angiogenic response. The bFGF pellets with anti-B61 antibodies had no effect on the angiogenic response. These results suggest that B61 plays a role in angiogenesis specific to the TNF-alpha induced pathway.

Pandey does not apply to the scenarios contemplated by the present invention for the following reasons. The authors of the reference clearly focus on the migration of cells and do not comment on the proliferation, growth and survival of cells, features contemplated by the present invention. Also, the entire system studied by the authors does not reflect the cellular environment consisting of hypoproliferative cells described within the present specification. The experimental model consists of situations wherein transplanted cellular material is induced into an angiogenic state by external agents such as TNF-alpha and bFGF. In fact, some of the experiments within the article actually demonstrate that in the absence of these exogenous triggers, the explanted cellular material remains dormant (See Fig 2, page 567 and Fig 4, page 568) further discounting the usefulness of this reference in the context of the contemplated invention.

In addition, the reference also comments on only one highly specific role of B61 in angiogenesis, namely in the TNF-alpha induced condition, as depletion of B61 had no effect on angiogenesis induced by exogenous bFGF. Moreover, the results in Figure 3 could be interpreted to support the use of antagonists to trigger proliferation of hypoproliferative cells. In Fig 3, HUVEC cells were untreated, treated with TNF-alpha, or treated with TNF-alpha + anti–B61 antibodies (columns 1, 2, and 3 respectively). Although the addition of anti-B61 antibodies inhibit the induced level of autophosphorylation triggered by TNF-alpha, it is possible, if one compares lane 1 and lane 3, that the treatment actually inhibits the basal phosphorylation of the Eck

receptor, an activity contemplated by the present invention (see section 5.5.2 of the present specification). Accordingly, Pandey clearly does not disparage and may even strengthen the therapeutic approach of targeting hypoproliferative cells with EphA2 antagonists to induce growth, proliferation and survival as encompassed by the present invention.

Rosenberg teaches that B61(Ephrin-A1) stimulation of Eck(EphA2) results in increased proliferation, enhanced barrier function and enhanced restitution of injured epithelial monolayers using the human colonic adenocarcinoma derived CaCo-2 cells as a model for human intestinal epithelium. Applicants respectfully submit that Rosenberg does not apply to the scenarios contemplated by the present invention for a number of reasons. The reference teaches the CaCo-2 cell model of epithelial remodeling and only provides a single figure demonstrating Eck and B61 expression in cancerous and normal human tissue (Fig 1). The authors use this evidence as support for the conclusions derived from all the other experiments performed in the study. Moreover, the authors readily admit that although the addition of B61 increased the growth rates of selected cancer cell lines including the CaCo-2 cells in the study, the addition of B61 had no effect on the growth rate of normal melanocytes and that B61 has been reported to have no effect on the mitogenesis of cultured endothelial cells (pg G831, col 1 para 1). Furthermore, the data in Figure 7 discloses that at lower concentrations of B61 (0.01 μg/ml), no growth stimulation is observed. It is only at higher and arguably less physiological concentrations (0.1 μg/ml and 1.0 μg/ml) that mitogenesis is observed. The authors further disclose that the adenocarcinoma derived CaCo-2 cell line will spontaneously differentiate two weeks after reaching confluence, suggesting that these cells retain additional abnormal cell cycle regulatory mechanisms (page G826, col. 1, para 3).

Contrary to the Examiner's allegations, the statements discussed above, being directed to hyperproliferative cancer cells, clearly emphasize the differences of the studies disclosed in Rosenberg as compared to the therapeutic approach of targeting hypoproliferative cells with EphA2 antagonists to induce growth, proliferation and survival as encompassed by the present invention. Accordingly, Applicants submit

that Rosenberg does not support the Examiner's position that the present invention would be ineffective.

In further response to the Examiner's statements regarding the uncertainty of the therapeutic approaches contemplated by the present invention, Applicants respectfully submit Brantley-Sieders *et al.* (Exhibit A: Brantley-Sieders *et al.* J Cell Sci. 117:2037-2049, hereinafter "Brantley-Sieders"), which clearly teaches a role for EphA2 in angiogenesis and endothelial cell survival *in vivo*. The teachings of Brantley-Sieders represent a comprehensive study of the role of EphA2 in endothelial cell migration and survival utilizing an EphA2 deficient (knockout) murine model. Specifically, the experiment depicted in Figure 8 (pg. 2047) demonstrates that EphA2 deficient endothelial cells are lost due to accelerated apoptosis when incubated *in vivo*. In fact, the authors also clearly state that "EphA2-deficient cells display decreased survival" (pg. 2045 col. 2, 1st para.) and "EphA2 RTK is also required for endothelial cell survival *in vivo*" (pg. 2045 col. 1, 2nd para.).

The teachings of Brantley-Sieders strongly support the scenario of the present invention, namely by demonstrating that functional EphA2 plays a role in angiogenesis mediated by endothelial cells. Furthermore, support for the present invention, namely promoting proliferation, growth and survival of a hypoproliferative cell is given by the evidence that EphA2 is downregulated as a result of dysregulated activity and coupled with the absence of EphA2 protein in many hypoproliferative environments (see above and Section 2 of the present specification). Accordingly, Applicants submit that the teachings of Brantley-Sieders correlate with the teachings of the specification in support of the present invention, specifically antagonizing EphA2 function to promote proliferation, growth and survival of hypoproliferative cells.

Complete predictability of success of experimentation is not required under the law. Although the Examiner has provided publications that attempt to refute the predictability of the clinical value of the methods of the invention, based on the arguments above, Applicants submit that the various scenarios presented do not apply to the present invention. As discussed previously, Pandey does not disparage and may support the rationale for antagonizing EphA2 function to induce proliferation,

growth and survival of hypoproliferative cells. The CaCo-2 model presented in Rosenberg does not apply to the present invention due to the hyperproliferative nature of the cell line as well as the aberrant regulation of differentiation. Moreover, Applicants submit that Brantley-Sieders clearly supports the role of EphA2 in angiogenesis and endothelial cell survival in an *in vivo* model, presenting a far more compelling argument in support of the present invention.

With regard to the term "antagonist", The Examiner maintains that the specification does not provide a sufficient enabling description of the claimed "antagonist" when the term is to include, but not be limited to, proteins, antibodies, nucleic acids, antisense, small molecule and carbohydrate. Applicants respectfully disagree.

At the time of filing, it would have been merely routine experimentation to assay antagonist candidates for the effects described in the specification. In *Wands*, the Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known" (858 F.2d at 740, 8 USPQ2d). As in *Wands,* the present invention may require *routine* assays to identify suitable antagonists with the properties described within the specification and should in no way be considered experimentation that is undue for one of ordinary skill in the art at the time of filing. Solely in an effort to expedite prosecution, Applicants have amended claims 1, 5, 6, 7, 10, 12-16, and 19 to recite methods using EphA2 antagonistic agents, wherein the antagonists are antibodies, and submit that the reasonable correlation between the scope of claims and scope of enablement test has been fully satisfied. Applicants respectfully request that this rejection be withdrawn.

Applicants respectfully submit that the specification clearly provides an enabling disclosure of what the functional limitations of the claims EphA2 antagonists would entail, and how to identify those antagonists. Specifically, sections 5.5, 5.5.1 – 5.5.4 of the present application provide clear guidance in a multitude of EphA2 functions to identify suitable antagonists. Applicants maintain that the procedures set forth in the sections 5.5.1-5.5.4 of the present application, such as

immunoprecipitation, Western Blot, ELISA, Tritium incorporation and CAT reporter assays, were well known to the ordinary artisan at the time of filing as evidenced by the many references cited. Furthermore, the specification teaches the ordinary artisan which characteristics of EphA2 function (for example, increased EphA2 gene expression/translation, increased EphA2 protein stability/accumulation, decreased cytoplasmic tail phosphorylation and the like) were to be targeted by antagonists of the invention. Coupled with the guidance within the specification, the ordinary artisan is directed through experimentation of the art accepted techniques referenced in the disclosure to aide in the identification of EphA2 antagonists as in *In re Colianni*.

In view of the teachings in the specification and the level of skill in the art at the time of filing, Applicants submit that the ordinary artisan would have readily been able to identify suitable antagonists of the present invention using the clear and directed guidance of the specification. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn.

The Examiner's Second Rejection Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn:

The Examiner has rejected claims 1-10, 12-16, and 17-23 based on U.S.C § 112, first paragraph as not complying with the written description requirement. Specifically, the Examiner states that the Applicants were not in possession of any "method of treating a hypoproliferative cell disorder or disorder involving increased cell death in a patient" and as such, the claimed invention was not adequately described by the disclosure present in the specification. Applicants respectfully disagree.

Applicants submit that the rejection is intended to encompass claims 1-10, 12-16, and 18-23 as claim 17 has been withdrawn from consideration as being drawn to a non-elected invention. Applicants also submit that the rejection with regard to claims 2-4, 8, 9, and 21-23 is moot in view of the cancellation of claims 2-4, 8, 9, and 21-23. Solely in an effort to expedite prosecution, Applicants have amended claims 1, 5, 6, 7, 10, 12-16, and 19. Applicants submit that the claim amendments are clearly

supported by disclosure throughout the specification as recited above and respectfully request that this rejection be withdrawn.

Applicants respectfully traverse the rejection and assert that the presently amended claims are adequately supported by the written description. Applicants submit that the written description requirement is met by disclosure of the "precise definition, such as by structure, formula, [or] chemical name' of the claimed subject matter sufficient to 'distinguish it from other materials' or by a representative number of species." *Regents of the University of California v. Eli Lilly & Co*, 119 F.3d 1559, 1568, 1569 (Fed.Cir. 1997). The *Lilly* standard was incorporated into the U.S. Patent and Trademark Office (U.S.P.T.O) Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1 "Written Description" Requirement ("the Guidelines") and the accompanying Synopsis. The Guidelines state that "the 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." The Synopsis provides examples for U.S.P.T.O Examiners to use to assess whether the written description requirement is met in various circumstances. There are 13 examples relating to the field of biotechnology. Example 16 relates to antibody technology. In Example 16, the Synopsis states, as previously discussed, that production of antibodies against a well-characterized antigen is "conventional" and that "[t]his is a mature technology where the level of skill is high and advanced." Furthermore, in *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004), the Federal Circuit held that:

> . . . as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen. *Id.*, at 1349.

Thus, the U.S.P.T.O acknowledges the advanced nature of the antibody art.

Also, The MPEP(8th ed. Aug 2001), 2164.01 states:

> A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and

Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Due to the well characterized properties of the EphA2 (Eck) antigen coupled with the advanced nature of the antibody art, Applicants assert that they are entitled to claims encompassing antagonistic EphA2 antibodies and methods of use thereof. EphA2 (Eck) was first sequenced and cloned in 1990 and as part of the study, antibodies were generated by immunizing rabbits with recombinant Eck (Lindberg *et al.* 1990, Mol. Cell. Biol. 10:6316-24). Many subsequent studies have utilized methods for generating antibodies against EphA2 including, for example, U.S. Patent No 6,927,203 (hereinafter "the '203 patent"). The '203 patent discloses the generation of at least 450 hybridomas specific for EphA2, of which the first four studied identified two distinct epitopes. Another study established a group of at least 44 hybridomas generated to the extracellular domain of EphA2 (Carles-Kinch *et al.* Cancer Research (2002) 62, 2840-2847), further demonstrating the well studied properties of the EphA2 antigen.

Applicants submit that given the well characterized nature of the EphA2 epitope, the specification clearly demonstrates that the Applicants were in possession of the claimed antibodies. Specifically, sections 5.2.1 and 5.2.1.1 describe antibody antagonists of EphA2, sections 5.2.1.2 and 5.2.3.1 describe methods of making and polynucleotides encoding antibody antagonists of EphA2, section 5.5 describe how to identify suitable antibody antagonists of EphA2 as well as section 5.6 which describes the therapeutic utility of antibody antagonists of EphA2. Applicants maintain that the specification is replete with teachings that provide ample guidance to the ordinary artisan to generate, identify and utilize antibody antagonists to the well characterized antigen, EphA2.

Based on the advanced state of antibody technology, as articulated by the U.S.P.T.O in the Synopsis, one of ordinary skill in the art would readily be able to produce antibodies to a well-defined antigen (see above), and select those particular antibodies having the required properties, using methods well described in the specification, and well-known in the art, without undue experimentation. Based on the advanced state of the antibody art, coupled with the more than adequate guidance

in the present specification, a skilled artisan would have recognized that the Applicants were in possession of the claimed antibodies. Accordingly, Applicants maintain that the present specification describes and shows possession of the claimed subject matter.

The Examiner's Rejection Under 35 U.S.C. § 102(a), Should Be Withdrawn:

The Examiner has rejected claims 1-2, 4-10 and 18-20 under 35 U.S.C. § 102(a) as being anticipated by U.S. Patent No. 5,824,303 (hereinafter "the '303 patent"). Specifically, the Examiner states that the method of using an Eck receptor binding protein (EBP) or a fragment thereof as a growth factor to stimulate proliferation of target cells anticipates the aforementioned claims. Applicants respectfully disagree.

A proper rejection of the claims requires the Examiner to show that each and every element as set forth in the claim is found, either expressly or inherently, in the asserted reference. (See, Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."). This has not been done. Applicants respectfully submit that the method of using an Eck binding protein to stimulate the proliferation of target cells does not completely encompass the present invention.

The '303 patent teaches the identification of EBP (EphrinA-1) and that EBP is capable of stimulating Eck (EphA2) receptor phosphorylation, crypt cell proliferation, neuron chemotaxis and neurite outgrowth. The '303 patent does not teach the use of EBP as an EphA2 antagonist. Moreover, Applicants maintain that the '303 patent does not teach the use of an EphA2 antagonist to treat a hypoproliferative cell disease or disorder involving increased cell death in a patient. Since each and every element of the rejected claims is not found in the '303 patent, as required under 35 U.S.C. § 102(a), reconsideration and withdrawal of the instant rejection is requested.

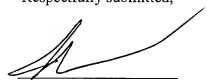
Solely in an effort to expedite prosecution, Applicants have amended claims 1, 5, 6, 7, 10, and 19 to read on the antibody class of EphA2 antagonists. Applicants

submit that the amended claims are not anticipated by the aforementioned reference which does not disclose the use of antibodies as Eck receptor antagonists and therefore request the removal of this rejection. Applicants also submit that the rejection with regard to claims 2, 4, 8, and 9 is moot in view of the cancellation of claims 2-4, 8, 9, 11, and 21-23.

CONCLUSION

Applicants respectfully request that the remarks of the present Response be entered and made of record in the present application. The application is believed to be in condition for allowance. Early notice to that effect is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below. If any additional fees are required in connection with this paper, please charge Deposit Account No. 500479 for the appropriate amount.

Respectfully submitted,



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